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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/556,833	04/21/00	CURRY	P 273012011100

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EXAMINER	
RAWLINGS,S	
ART UNIT	**PAPER NUMBER**
1642	11

DATE MAILED: 11/06/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/556,833	CURRY ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 August 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *17-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-21* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The amendment filed on August 15, 2001 in Paper No. 10 is acknowledged and has been entered.

2. Claims 1-21 are pending in the application. Claims 17-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 6.

3. Claims 1-16 are currently under prosecution.

Oath/Declaration

4. In the previous Office Action mailed on April 10, 2001 (Paper No. 8), the Examiner objected to the declaration. Applicants' response in Paper No. 10 is acknowledged. Upon consideration of the record the objection is withdrawn.

Drawings

5. In the previous Office Action mailed on April 10, 2001 (Paper No. 8), the Examiner objected to the drawings. In Paper No. 10, Applicants request that the objection be held in abeyance pending an indication of allowable subject matter in the application. In response to Applicants' request, formal correction of the noted defect can be deferred until the allowance of the application.

Specification

6. The disclosure is objected to because of the following informalities:

(a) On page 3, "photodynamic" is misspelled in line 20.

(b) On page 10, the disclosure inconsistently refers to various photosensitizers, e.g., BPD_MA (line 18) and BPD-MA (line 21), which are presumably the same agent.

(c) Throughout the disclosure italicized words and phrases are typed as subscript.

Appropriate correction is required.

7. The disclosure is objected to because the disclosure refers to embedded hyperlinks and/or other forms of browser-executable code, which are impermissible and require deletion.

The attempt to incorporate subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP § 608.01(p), paragraph I regarding incorporation by reference.

Response to Amendment and Remarks

8. Applicant's arguments with respect to claims 1-16 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-16 are indefinite because claims 1, 2, and 3 recite the phrase "effective amounts". The phrase "effective amounts" is indefinite when the claims fail to state the functions that are to be achieved. See *In re Frederiksen & Nielsen*, 213 F 2d 547, 102 USPQ 35 (CCPA 1954). Accordingly, one of ordinary skill in the art is not reasonably apprised of the metes and bounds of the invention.

Claims 1-16 are indefinite because claims 1, 2, and 3 recite the phrase "irradiating said subject with light absorbed by said photosensitizer". Recitation of the

phrase renders the claims indefinite because it is unclear how light, which is absorbed by a photosensitizer, can be used to irradiate a subject. Accordingly, one of ordinary skill in the art is not reasonably apprised of the metes and bounds of the invention. Amending the claims to more particularly point out and distinctly claim the subject matter that Applicants regard as the invention can obviate this rejection.

Claims 1-16 are indefinite because claims 1, 2, and 3 fail to recite a positive process step that clearly relates back to the preamble of the claims. Accordingly, one of ordinary skill in the art is not reasonably apprised of the metes and bounds of the invention. Amending claim 1, for example, to recite the phrase "whereby said subject is treated" at the end of the last line can obviate this rejection with respect to claim 1. Similar amendments to claims 2 and 3 can obviate the rejection with respect to those claims.

Claims 1-16 are indefinite because claims 1, 2, and 3 recite the phrase "a component derived from lipid A of a bacterial lipopolysaccharide". Recitation of the phrase renders the claims indefinite because it cannot be ascertained to what component derived from lipid A the claims refer. For example, it is unclear whether the claim is meant to be directed to a derivative of lipid A, as the specification would suggest, or to any component of lipid A, such as a portion of the hydrocarbon backbone. Accordingly, one of ordinary skill in the art is not reasonably apprised of the metes and bounds of the invention.

Claims 1, 2, and 4-16 are vague and indefinite because claims 1 and 2 recite the term "metastatic tumors". Recitation of the term renders the claim vague and indefinite because it cannot be ascertained from the claim or from the disclosure whether the term is meant to refer to any tumor with metastatic potential or any metastasis (i.e., a secondary tumor that has developed by the spreading of tumor cells from a primary point of origin to a distant anatomical site). Accordingly, one of ordinary skill in the art is not reasonably apprised of the metes and bounds of the invention. This issue is particularly important because it is noted that in the response to the previous Office Action, Applicants' attempt to differentiate the instant invention from the prior art by suggesting, "the instant claims are directed to the treatment of 'metastatic tumors' which

are not the same as the non-metastatic tumors treated by Korbelik et al." (Paper No. 10, page 8, paragraph 6). However, EMT6 is a transplantable mouse mammary tumor cell line that has been utilized widely as a model system to study the effects of various treatments on local tumor growth *and pulmonary metastasis*. While Korbelik, et al (cited in the previous Office Action) did not specifically determine whether their method of treatment prevented the development of metastases in the lung or other anatomical site remote to the implantation site, it is clear that their method results in the effective inhibition of the primary metastatic tumor, a therapeutic effect which would be reasonably expected to limit the number of metastases.

Claims 2, 4-7, and 10-15 are indefinite because claim 2 recites the phrase "a subject at risk for developing metastatic tumors". Recitation of the phrase renders the claim indefinite because it is unclear to whom the claim refers, because the requisite degree of risk is not defined by the claim or the specification. Moreover, the specification does not provide a standard for ascertaining whether or when a subject is "at risk" and is also void of guidance indicating how one can determine or know when a subject is "at risk". Accordingly, one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claims 5-7 are vague and indefinite because the claims recite the term "mg/kg". Recitation of the term renders the claims vague and indefinite because it is unclear to what subject matter the units of mass, i.e., milligrams (mg) and kilograms (kg), refer. Accordingly, one of ordinary skill in the art is not reasonably apprised of the metes and bounds of the invention. Amending the claims, for example, to recite in place of the term "mg/kg", the phrase "milligrams of photosensitzer per kilogram of the subject's body weight" can obviate this rejection.

Claim 11 is indefinite because the language and the punctuation used in the claim cause the claim to be confusing. Amending the claim to recite, for example, the limitation "wherein said photosensitizer is administered to the subject and the subject is irradiated before the immuno-adjuvant is administered to the subject" can obviate this rejection.

Claim 15 is vague and indefinite because the claim recites the term "improves". The term "improves" is a relative term that renders the claim indefinite, because the term is not defined by the claim and the specification does not provide a standard for ascertaining the requisite degree. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention. Amending the claim to recite the specific degree to which the claim requires the additional irradiation to improve penetration of the absorbed light can obviate this rejection. However, Applicant is cautioned against the introduction of new matter into the specification, including the claims, by amendment.

Claim 15 is vague and indefinite because the claim recites the phrase "with light of a wavelength which improves penetration of the absorbed light". Recitation of the phrase renders the claim vague and indefinite because it is unclear to into what matter the claim requires the irradiation to improve penetration. It is also unclear to what absorbed light the claim requires an improvement in penetration. Furthermore, it is noted that neither the claim nor the specification disclose to what wavelength of light, which when used to irradiate the undisclosed subject matter improves the penetration of the "absorbed light", the claim refers. Accordingly, one of ordinary skill in the art is not reasonably apprised of the metes and bounds of the invention.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 6,290,712-B1 in view of US Patent Nos. 4,436,727-A, 4,912,094-A, 5,149,527-A, 5,579,554-A, 5,770,619-A, 5,929,105-A, 5,990,149-A, 6,071,944-A, and 6,071,944-A.

The claims are drawn to a method for treating, preventing, or inhibiting primary or metastatic tumors or the development thereof in a subject, said method comprising administering to the subject a green porphyrin photosensitizer and an immunoadjuvant comprising mycobacterial cell wall extract (MCWE) and/or a derivative of bacterial lipopolysaccharide (LPS) lipid A and irradiating the subject with light of a wavelength absorbed by said photosensitizer, wherein said photosensitizer is a benzoporphyrin derivative (BPD) administered intravenously or intratumorally before irradiation of the subject as a dose ranging from 0.05 to 10 mg/kg body weight, wherein said irradiation is localized to the tumors, wherein said immunoadjuvant is administered systemically.

According to the claims, the BPD can be BPD-MA, EA6, or B3. Furthermore, the claimed method can further comprise an additional irradiation with light of a wavelength that improves penetration of the absorbed light before irradiating the subject at the wavelength absorbed by the photosensitizer.

US Patent No. 6,290,712-B1 teaches a method for treating a malignant tumor in a human or other animal, which comprises administering to the subject a chromophore (i.e., photosensitizer) and an immunoadjuvant and then irradiating the tumor at a wavelength sufficient to induce the destruction of the tumor and to stimulate the immune system so that further neoplastic cellular proliferation in the subject is prevented or inhibited (abstract). For clarification, the term "malignant" is used to describe a tumor that is anaplastic, invasive, and metastatic; that is, it has primitive cellular growth characterized by a lack of differentiation, it moves into and destroys surrounding tissue, and it spreads to other parts of the body. Therefore, a characteristic of all malignant tumors is the capacity to metastasize. In this regard, US Patent No. 6,290,712-B1 teaches, "it is an object of this invention to improve the treatment of neoplasms by combining photodynamic and immunologic therapies in such a way as to cause immediate neoplastic cellular destruction while concomitantly stimulating the self-immunological defense system against proliferation of residual or metastatic cells" (column 5, lines 24-29). While '712 exemplifies the use of a particular photosensitizer, namely indocyanine green, other suitable photosensitizers are disclosed (column 7, lines 36-60); specifically, '712 teaches that upon absorption of a particular wavelength of light, suitable photosensitizers should have the ability "to create thermal energy, to evolve singlet oxygen and other active molecules, or to be toxic in their own right" (lines 40-43). '712 exemplifies the use of modified chitosan as the immunoadjuvant, but discloses that other immunoadjuvants that non-specifically stimulate the immune system can be also be used, including those comprising a component of bacterial cell walls (column 9, lines 10-15). '712 teaches that both the photosensitizer and the immunoadjuvant can be administered intratumorally (for example, column 15, lines 10-20), but also discloses that the photosensitizer can be administered systemically (column 2, lines 26-28). '712 teaches that their method has several advantages over

conventional and unconventional treatment modalities, but the "combination of sensitizer and immune-stimulation adjuvant is the key" (column 5, lines 63-65). '712 concludes, the "most significant advantage is a combined acute and chronic tumor destruction" (column 5, lines 65 and 66).

However, US Patent No. 6,290,712-B1 does not explicitly disclose that a suitable photosensitizer is a "green porphyrin" or benzoporphyrin derivative (BPD), namely BPD-MA, EA6, or B3. In addition, '712 does not explicitly teach that the amount of photosensitizer administered to the subject can range between 0.05 and 10 mg/kg of body weight or that the subject can be treated with the photosensitizer and irradiated before the immunoadjuvant is administered. '712 does not explicitly disclose that the immunoadjuvant can comprise mycobacterial cell wall extracts and/or de-3-O-acylated lipid A. Also, '712 does not explicitly disclose that the subject may have undergone previous therapeutic treatment for cancer or that the immunoadjuvant can be administered systemically. Finally, '712 does not disclose that the method can comprise an additional step in which the subject is irradiated at a wavelength that improves the penetration of absorbed light before the subject is irradiated at the wavelength at which the photosensitizer absorbs light.

US Patent No. 5,770,619-A teaches a method for administering photodynamic therapy to a subject in order to effectively destroy a solid tumor (abstract; claims). '619 teaches that the method comprises administering to a subject either locally or systemically a benzoporphyrin derivative (BPD), namely BPD-MA and then irradiating at least a portion of the subject at a wavelength that is sufficient to photoactivate BPD-MA (column 3, lines 20-54). '619 discloses an advantage is gained in using BPD, because "BPD also has demonstrated a higher affinity for tumor tissue, including leukemic cells, than for normal non-malignant cells" (column 1, lines 59-61). '619 also discloses that the photosensitizer can be administered intravenously for systemic delivery or topically for localized delivery (column 5, lines 59-65) at doses that range from 0.5 to 2.0 mg/kg of body weight (Figure 1). However, with regard to the appropriate and effective dose, '619 teaches:

> This invention is the conduct of effective PDT [photodynamic therapy] more safely and with fewer adverse effects because the post injection interval is much shorter and doses of both the photosensitive agent and light are halved. In contrast, previously it was thought that the photosensitizer initially distributed nonselectively throughout the body and that it took several hours to days for the photosensitizer to accumulate selectively in the target tissue. It was thought that selective distribution occurred gradually, with a considerable amount of exchange between the target tissue and the pool of circulating photosensitizer molecules. Thus, it was considered essential to delay post injection light treatment by several hours to days (column 6, lines 53-64).
>
> These two surprising results encouraged testing of early, lower dose illumination in tumor treatment with PDT (i.e., before photosensitizers permeate skin or other normal tissue). Experimental evidence (presented below) in mice indicates the inventive method is safe and effective (column 7, lines 30-34).

US Patent No. 5,990,149-A teaches the synthesis of another suitable benzoporphyrin derivative, namely B3, which is a potent photosensitizer and can therefore substitute for BPD-MA. '149 specifically discloses, "BPD-MA was found to have particularly useful properties for PDT and is currently in clinical development. However, there remains a need for additional specific forms of photoactive agents which expand the repertoire of photoactive compounds for the variety of indications to which PDT is applied" (column 1, lines 62-66).

US Patent No. 5,929,105-A also teaches a method for photodynamic therapy of cancer, wherein benzoporphyrin derivatives, namely the isomers A-EA6 and B-EA6 are administered to the subject (claims). '105 teaches that A-EA6 has a stronger immunomodulatory effect than BPD-MA (column 13, lines 34-36). Furthermore, '105 discloses that B-EA6 does not accumulate in non-tumor tissue, whereas BPD-MA accumulates in the skin within the first three hours following administration of the photosensitizers to the subject (column 7, lines 56-58). Moreover, as compared to BPD-MA, '105 discloses an additional advantage in using EA6, which is that B-EA6 clears more rapidly from all normal tissues while specifically accumulating in the tumors, which is of benefit because B-EA6 will have less non-specific toxicity and can therefore be more safely administered to the subject (column 7, lines 41-45 and 59-61; column 10, lines 18-20).

US Patent No. 5,149,527-A teaches that an immunopotentiating protocol, which causes the death or regression of developing tumors in subjects in whom previously

received antitumor therapy resulted in the successful destruction of the tumor or parts thereof, wherein an immunoadjuvant is administered to the subject at a time after the previous therapy when formation of tumor-specific macrophages has occurred as the result of the primary tumor's destruction (abstract). '527 discloses the following:

> The invention is directed to protocols for effecting tumor regression and/or necrosis in animal subjects. In particular, it involves pretreatment of the tumor with a tumor destroying protocol, such as a chemotherapeutic agent, radiation, or hyperthermia, for a time and in a manner effective to cause the formation of tumor-specific cytotoxic macrophages and other tumor infiltrating effector cells and then to administer a quantity of immunopotentiator specific for these macrophages which effectively results in lysis of the tumor. Essentially, the tumor-destructive protocol that precedes treatment with immunopotentiator is used to provide "vaccination in situ" (column 2, lines 25-38).

'527 discloses that localized antitumor therapy, e.g., photodynamic therapy, is "usually effective to produce at least partial destruction of the neoplasm" (page 3, lines 24-26). Furthermore, '527 teaches that a wide variety of immunoadjuvants can be used in the protocol provided that the agent is capable of stimulating macrophages and can be administered locally or systemically by intravenous injection (Figure 1; column 4, lines 42-56; column 5, lines 15-23). While '527 does not explicitly teach that immunoadjuvants comprising modified chitosan can be used to stimulate tumor-destructive macrophages, it does disclose that mycobacterial cell wall extracts and detoxified lipopolysaccharide (e.g., monophosphoryl lipid A) are suitable (Figure 1).

US Patent No. 5,579,554-A teaches an effective means for treating cancer, which comprises administering to the subject in need of therapy an immunoadjuvant composed of modified mycobacterial cell wall extract (abstract). '554 discloses, "[t]he present invention is also effective in treating various cancers that occur in both humans and animals. The cancers can be primary or metastatic" (column 3, lines 42-45). The advantage that '554 provides is that the immunoadjuvant is effective but does not need to be suspended in oil and therefore its use precludes the development of granulomas in subjects treated with immunoadjuvants comprising oil (column 4, lines 5-9; column 2, lines 39-42). '554 teaches the following:

> The present invention relates to an aqueous suspension of a mycobacterial cell wall extract that is effective in treating the immune system in animals and humans. The aqueous suspension can optionally have glycosaminoglycans, such as hyaluronic acid, as a component. The present invention is an aqueous preparation of modified bacterial

> cell walls that does not contain any oil or oil-like substances. Because there is no oil in the aqueous suspension of the mycobacterial cell wall extract that comprises the present invention, the unwanted side effects that are present in the cell wall preparations that are in the prior art are eliminated. The aqueous suspension of the mycobacterial cell wall extract is capable of stimulating the immune system of an animal or human, thereby causing the body to neutralize or abort an infection or retard or eliminate the growth of a cancer (column 1, lines 8-15).

Furthermore, to explain the beneficial effects of the immunoadjuvants, '554 discloses:

> Whether large complex molecules like peptidoglycans or lipopolysaccharides or simple molecules such as muramyl dipeptide are used, the common pathway points to macrophage activation as the mechanism of adjuvant activity. The stimulation of macrophages by adjuvants results in increased antigen uptake, enhanced cytotoxicity, phagocytosis, hydrogen peroxide production, arachidonic acid metabolism, enzyme degranulation, and the synthesis and release of polypeptide monokines. The polypeptide monokines play an important role because they possess potent biological properties for various cells. To date, these monokines include interleukin 1, alpha interferon, tumor necrosis factor (cachectin), and colony-stimulating factors. Each monokine can, in turn, trigger other cells to produce biologically active cytokines (column 2, lines 15-29).

In addition, '554 teaches that the aqueous mycobacterial cell wall extract can be injected directly into the tumor or it can be given systemically (column 5, lines 14-24).

Thus, at the time the invention was made, it was well known in the art that lipid A is the lipid fraction of lipopolysaccharide (LPS), which is ordinarily obtained from Gram-negative bacteria. Furthermore, numerous studies had demonstrated that most or all of the potent immunoadjuvant activity of Gram-negative bacterial endotoxin (i.e., LPS) resides in the lipid A moiety of LPS. While LPS or the lipid A fraction thereof is too toxic to be used as an adjuvant for treatment of humans and other animals, modified lipid A, such as monophosphoryl lipid A was known to be less toxic than the unphosphorylated lipid and was therefore commonly used as an non-specific immunostimulant at the time the invention was made. In this regard, US Patent No. 4,912,094-A teaches that modified lipopolysaccharides, particularly de-3-O-acylated monophosphoryl lipid A and de-3-O-acylated diphosphoryl lipid A retain a high level of immunostimulating capacity but have the advantage of being considerably less endotoxic than naturally occurring lipopolysaccharide (abstract).

US Patent No. 4,436,727-A also teaches an immunoadjuvant comprised of a detoxified endotoxin (i.e., LPS) product, which when combined with mycobacterial cell wall skeleton extracts, can be used as an effective means for treating a subject

diagnosed with cancer (abstract). '727 teaches that the combination of immunoadjuvants is more effective than the detoxified endotoxin alone (column 6, lines 30-45).

US Patent No. 6,071,944-A teaches a method for treatment of malignant melanoma, which also comprises administering to the subject a photosensitizer and then irradiating the subject at a wavelength at which the photosensitizer absorbs light. '944 discloses that the efficacy of photodynamic therapy can be hampered if lesions are pigmented, which is often the case with highly metastatic melanoma, because the pigmented tumor cells are less responsive; the lack of response attributed to optic filtering by melanin granules within the cells (column As a solution to the problem, '944 teaches that pretreatment of pigmented tumors with high peak power light (such as 1064 nm light) enhances their susceptibility to conventional photodynamic therapy (column). Therefore, '944 teaches that photodynamic therapy is more efficacious when the subject is irradiated at a wavelength that improves penetration of the wavelength of light at which the photosensitizer absorbs.

In view of the teachings of US Patents Nos. 4,436,727-A, 4,912,094-A, 5,149,527-A, 5,579,554-A, 5,770,619-A, 5,929,105-A, 5,990,149-A, and 6,071,944-A, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to improve the method of US Patent No. 6,290,712-B1 to derive a method for treating, preventing, or inhibiting primary or metastatic tumors or the development thereof in a subject, said method comprising administering to the subject a green porphyrin photosensitizer, namely BPD-MA or B3, or more particularly EA6, and an immunoadjuvant comprising mycobacterial cell wall extract (MCWE) and/or a derivative of bacterial lipopolysaccharide (LPS) lipid A and irradiating the subject with light of a wavelength absorbed by said photosensitizer, wherein said photosensitizer can be administered intravenously or intratumorally before irradiation of the subject at a dose ranging from 0.05 to 10 mg/kg body weight, wherein said irradiation can be localized to the tumors, and wherein said immunoadjuvant can be administered systemically.

US Patent No. 6,290,712-B1 teaches an effective method for treating a malignant tumor in a human or other animal, which comprises administering to the subject a photosensitizer, namely indocyanine green or another suitable photosensitizers that upon absorption of a particular wavelength of light, has the ability to create thermal energy, to evolve singlet oxygen and other active molecules, or to be toxic in their own right, and an immunoadjuvant, namely an immunoadjuvant derived from chitosan, and then irradiating the tumor at a wavelength sufficient to induce at least the partial destruction of the tumor and to thereby stimulate the immune system in the presence of the immunoadjuvant so that further destruction of the tumor will result and also further neoplastic cellular proliferation in the subject will be prevented or inhibited. In view of the teachings of US Patent No. 5,770,619-A, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute BPD-MA for the photosensitizer of '712, because '619 discloses an advantage is gained in using BPD, namely BPD has a higher affinity for tumor tissue than for normal non-malignant cells; and besides, '712 teaches that BPD is a suitable photosensitizer since BPD has the ability to create thermal energy, to evolve singlet oxygen and other active molecules, or to be toxic in their own right upon absorption of a particular wavelength of light. Moreover, '619 teaches that lower dosages of BPD can be administered to subjects while still achieving therapeutic benefit, which is an advantageous since photosensitizers are toxic compounds and therefore limiting the necessary dosage is desirable. According to the teachings of US Patent No. 5,990,149-A B3, which is also potent BPD photosensitizer can substitute for BPD-MA. However, it view of the teachings of US Patent No. 5,929,105-A, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the green porphyrins A-EA6 or B-EA6 for the photosensitizer of '712, because '105 teaches that A-EA6 has a stronger immunomodulatory effect than BPD-MA and B-EA6 does not accumulate in non-tumor tissue, whereas BPD-MA accumulates in the skin within the first three hours following administration of the photosensitizers to the subject. Moreover, as compared to BPD-MA, '105 discloses an additional advantage in using EA6, which is that B-EA6 clears more rapidly from all normal tissues while specifically

accumulating in the tumors, which is of benefit because B-EA6 will have less non-specific toxicity and can therefore be more safely administered to the subject.

In view of the teachings of US Patent No. 5,149,527-A, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute an adjuvant that is disclosed as being capable of stimulating macrophages, namely a detoxified derivative of mycobacterial cell wall extract, such as that taught by US Patent No. 5,579,554-A, or a detoxified lipid A derivative, such as that taught by US Patent No. 4,912,094-A, for the immunoadjuvant of '712, because '527 discloses that an immunoadjuvant that is administered to the subject at a time after the previous successful therapy, when formation of tumor-specific macrophages is occurring as the result of the primary tumor's destruction, causes the death or regression of developing tumors in subjects. While '527 does not explicitly teach that immunoadjuvants comprising modified chitosan, such as the immunoadjuvant of '712, can be used to stimulate tumor-destructive macrophages; however, '527 does disclose that mycobacterial cell wall extracts and detoxified lipopolysaccharide are suitable. US Patent No. 5,579,554-A teaches an effective immunoadjuvant composed of modified mycobacterial cell wall extract (MCWE), which stimulates macrophages and which can be used to treat a patient diagnosed with a primary or metastatic (i.e., secondary) tumor. According to the disclosure of '554, the advantage of using MCWE is that the immunoadjuvant can be administered systemically or locally in an aqueous form; therefore its use precludes the development of granulomas in subjects, which is an adverse effect of treating subjects with immunoadjuvant comprising oil. Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the modified MCWE of '554 for the immunoadjuvant of '712. Alternatively, based upon the teachings of '527, it also would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the modified LPS, particularly de-3-O-acylated monophosphoryl lipid A of '554, for the immunoadjuvant of '712, because '527 indicates that modified lipid A is also capable of stimulating macrophages and de-3-O-acylated diphosphoryl lipid A retains a high level of immunostimulating capacity, but have the advantage of being

considerably less endotoxic than other naturally occurring and modified LPS derivatives. Finally, in view of US Patent No. 4,436,727-A, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute a combination of modified BCWE and modified LPS, particularly de-3-O-acylated monophosphoryl lipid A of '554, for the immunoadjuvant of '712, because '727 teaches an immunoadjuvant comprised of combination of a detoxified LPS product and detoxified mycobacterial cell wall skeleton extract can be used as an effective means for treating a subject diagnosed with cancer, but moreover '727 teaches that the combination of immunoadjuvants is more effective than one of immunoadjuvants alone.

Furthermore, in view of US Patent No. 6,071,944-A, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to further modify the improved method of US Patent No. 6,290,712-B1 to the claimed method can further comprise an additional irradiation with light of a wavelength that improves penetration of the absorbed light before irradiating the subject at the wavelength absorbed by the photosensitizer, because '944 teaches that photodynamic therapy is more efficacious when the subject is first irradiated at a wavelength that improves penetration of the wavelength of light at which the photosensitizer absorbs, especially if the tumor cells are pigmented.

In view of the teachings of US Patents Nos. 4,436,727-A, 4,912,094-A, 5,149,527-A, 5,579,554-A, 5,770,619-A, 5,929,105-A, 5,990,149-A, and 6,071,944-A, one of ordinary skill in the art would have been motivated to improve the method of US Patent No. 6,290,712-B1 because there was a long-felt need at the time for more efficacious therapeutic means for treating, preventing, or inhibiting primary and secondary cancers in humans and other animals.

Conclusion

13. No claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is

(703) 305-3008. The examiner can normally be reached on Monday-Thursday, alternate Fridays, 8:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
November 4, 2001

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